Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Esmeron 10 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 10 mg rocuronium bromide.

Each 2.5 ml vial contains 25 mg rocuronium bromide.
Each 5 ml vial contains 50 mg rocuronium bromide.
Each 10 ml vial contains 100 mg rocuronium bromide

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless to slightly yellow/brown, sterile, aqueous solution.

pH: 3.8 - 4.2

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Esmeron is indicated in adult and paediatric patients (from term neonates to adolescents [0 to <18 years]) as an adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation, during surgery. In adults, Esmeron is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

4.2 Posology and method of administration

Like other neuromuscular blocking agents, Esmeron should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.

As with other neuromuscular blocking agents, the dosage of Esmeron should be individualised in each patient. The method of anesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other drugs that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Esmeron. This potentiation, however, only becomes clinically relevant in the course of anaesthesia when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Esmeron should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Esmeron during long lasting procedures (longer than 1 hour) under inhalational anaesthesia. (see section 4.5)

In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical Procedures

Tracheal intubation:
The standard intubating dose during routine anesthesia is 0.6 $mg.kg^{-1}$ rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 $mg.kg^{-1}$ rocuronium bromide is recommended

for facilitating tracheal intubation conditions during rapid sequence induction of anesthesia, after which adequate intubation conditions are also established within 60 seconds in nearly all patients. If a dose of 0.6 mg.kg^{-1} rocuronium bromide is used for rapid sequence induction of anesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.
For use of rocuronium bromide during rapid sequence induction of anesthesia in patients undergoing Caesarean section reference is made to section 4.6.

Maintenance dosing:
The recommended maintenance dose is 0.15 mg.kg^{-1} rocuronium bromide; in case of long-term inhalational anaesthesia this should be reduced to 0.075-0.1mg.kg^{-1}rocuronium bromide.
The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height,or when 2 to 3 responses to train of four stimulation are present.

Continuous infusion:
If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg.kg^{-1} rocuronium bromide and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg.kg^{-1}.h^{-1} and under inhalational anaesthesia the infusion ranges from 0.3-0.4mg.kg^{-1}.h^{-1}.Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric patients:
For neonates (0-27 days), infants (28 days – 2 months), toddlers (3-23 months), children (2-11 years) and adolescents (12-17 years) the recommended intubation dose during routine anesthesia and maintenance dose are similar to those in adults. However, the duration of action of the single intubating dose will be longer in neonates and infants than in children (see section 5.1)

For continuous infusion in paediatrics, the infusion rates, with exception of children (2-11 years), are the same as for adults. For children aged 2-11 years, higher infusion rates might be necessary. Thus for children (2-11years), the same initial infusion rates as for adults are recommended and then this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure.

The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure:
The standard intubation dose for geriatric patients (>65 years) and patients with hepatic and/or biliary tract disease and/or renal failure during routine anesthesia is 0.6 mg.kg^{-1} rocuronium bromide. A dose of 0.6 mg.kg^{-1} rocuronium bromide should be considered for rapid sequence induction of anesthesia in patients in which a prolonged duration of action is expected. Regardless of the anesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg.kg^{-1} rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg.kg^{-1}.h^{-1}. (see Continuous infusion) (See also section 4.4.).

Overweight and obese patients:
When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.

Intensive Care Procedures

Tracheal intubation:
For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance dosing:
The use of an initial loading dose of 0.6 mg.kg^{-1} rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 - 90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3 - 0.6 mg.kg^{-1}.h^{-1} during the first

hour of administration, which will need to be decreased during the following 6 - 12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2 - 0.5 $mg.kg^{-1}.h^{-1}$ depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Special populations:
Esmeron is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Administration
Esmeron is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

4.4 Special warnings and precautions for use

Esmeron should be administered only by anaesthetists familiar with the use of neuromuscular blocking agents, and when facilities for controlled ventilation, insufflation with oxygen and tracheal intubation are available for immediate use.

Appropriate Administration and Monitoring
Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. In the case of intubation difficulties resulting in a clinical need for immediate reversal of rocuronium induced neuromuscular block, the use of a reversal agent should be considered. It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

Residual Curarization
As with other neuromuscular blocking agents, residual curarization has been reported for Esmeron. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent (such as sugammadex or acetylcholinesterase inhibitors) should be considered, especially in those cases where residual curarization is more likely to occur.

Anaphylaxis
Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Long-term Use in an Intensive care Unit
In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under the supervision of experienced clinicians who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long term administration of other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

Use with Suxamethonium

If suxamethonium is used for intubation, the administration of Esmeron should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Because rocuronium bromide is always used with other drugs and because of the risk of malignant hyperthermia during anesthesia, even in the absence of known triggering factors, physicians should be aware of the early symptoms, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of anesthesia. Animal studies have shown that rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with ESMERON have been observed through post-marketing surveillance however, the causal association has not been proven.

Hypertensive crisis in patients with phaeochromocytoma
Postmarketing data have identified cases of hypertensive crisis temporally related to administration of rocuronium in patients with diagnosed or latent phaeochromocytoma. Rocuronium should therefore be used with caution in such patients.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:

Hepatic and/or biliary tract disease and renal failure
Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 $mg.kg^{-1}$ rocuronium bromide.

Prolonged circulation time
Conditions associated with prolonged circulation time such as cardiovascular disease, old age and oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.

Neuromuscular disease
Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response.

Hypothermia
In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged.

Obesity
Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight.

Burns
Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response**.**

Conditions which may increase the effects of Esmeron
Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia, cachexia.
Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially `sodium-free'. To be taken into consideration in patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents.

Increased effect:

- Halogenated volatile anaesthetics potentiate the neuromuscular block of Esmeron. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.4).
- Long-term concomitant use of corticosteroids and Esmeron in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8)

Other drugs:

- antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anesthetics (lidocaine i.v., bupivacaine epidural), and acute administration of phenytoin and β-blocking agents.

Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4)

Decreased effect:

- Prior chronic administration of phenytoin or carbamazepine.
- Protease inhibitors (gabexate, ulinastatin)
- Neostigmine, edrophonium, pyridostigmine

Variable effect:

- Administration of other non-depolarizing neuromuscular blocking agents in combination with Esmeron may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
- Suxamethonium given after the administration of Esmeron may produce potentiation or attenuation of the neuromuscular blocking effect of Esmeron.

Effect of Esmeron on other drugs
Esmeron combined with lidocaine may result in a quicker onset of action of lidocaine.

Paediatric Patients

No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use (see section 4.4) should also be taken into account for paediatric patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing Esmeron to pregnant women.

Caesarean section
In patients undergoing Caesarean section, Esmeron can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. Esmeron, administered in doses of 0.6mg.kg^{-1}, has been shown to be safe in patients undergoing Caesarean section.Esmeron does not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the newborn.

Note 1: doses of 1.0 mg.kg^{-1} have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg.kg^{-1} is recommended in this patient group.

Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of Esmeron should be reduced and be titrated to twitch response.

Lactation

It is unknown whether Esmeron is excreted in human breast milk. Animal studies have shown insignificant levels of Esmeron in breast milk. Esmeron should be given to lactating women only when the attending physician decides that the benefits outweigh the risks. After the administration of a single dose, it is recommended to abstain from next breastfeeding for five elimination half-lives of rocuronium, i.e. for about 6 hours.

4.7 Effects on ability to drive and use machines

Since Esmeron is used as an adjunct to general anesthesia, the usual precautionary measures after a general anesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

MedDRA SOC	Preferred Term[1]		
	Uncommon/rare[2] (<1/100, >1/10 000)	Very rare (<1/10 000)	Not Known
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Eye disorders			Mydriasis[3] Fixed pupils[3]
Cardiac disorders	Tachycardia		Kounis Syndrome
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Skin and subcutaneous tissue disorders		Angioneurotic edema Urticaria Rash Erythematous rash	
Musculoskeletal and connective tissue disorders		Muscular weakness[4] Steroid myopathy[4]	
General disorders and administration site conditions	Drug ineffective Drug effect/therapeutic response decrease Drug effect/therapeutic response increased Injection site pain Injection site reaction	Face oedema	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anesthesia	

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[1] Frequencies are estimated derived from post-marketing surveillance reports and data from the general literature.

[2] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories.

[3] In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).
[4] After long-term use in the ICU

Anaphylactic reactions
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. Anaphylactic/anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions.

Histamine release and histaminoid reactions
Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9 $mg.kg^{-1}$ rocuronium bromide.

In postmarketing reports, hypersensitivity has been observed for rocuronium as well as for rocuronium-sugammadex complex.

Prolonged neuromuscular block
The most frequent adverse reaction to non-depolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea.

Myopathy
Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see section 4.4).

Local injection site reactions
During rapid sequence induction of anaesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Paediatric patients
A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide (up to 1 mg /kg) showed that tachycardia was identified as adverse drug reaction with a frequency of 1.4%.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. There are two options for the reversal of neuromuscular block: (1) Sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Esmeron, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED90 (135 $mg.kg^{-1}$ rocuronium bromide) was administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code)
Muscle relaxants, peripherally acting agents. ATC code: M03AC09

Mechanism of action
Esmeron (rocuronium bromide) is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects
The ED90 (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0.3 $mg.kg^{-1}$ rocuronium bromide. The ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40 respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6$mg.kg^{-1}$ rocuronium bromide is 30-40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6 $mg.kg^{-1}$ rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45 $mg.kg^{-1}$ rocuronium bromide, (1-1.5 x ED 90), onset of action is slower and duration of action is shorter.
With high doses of 2 $mg.kg^{-1}$, clinical duration is 110 minutes.

Intubation during routine anesthesia
Within 60 seconds following intravenous administration of a dose of 0.6 $mg.kg^{-1}$ rocuronium bromide (2 x ED90 under balanced anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established within 2 minutes. After administration of 0.45 mg rocuronium bromide per kg body weight, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction
During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0$mg.kg^{-1}$ rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following a dose of 0.6$mg.kg^{-1}$ rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Paediatric Patients
Mean onset time in infants, toddlers and children at an intubation dose of 0.6 $mg.kg^{-1}$ is slightly shorter than in adults. Comparison within paediatric age groups showed that the mean onset time in neonates and adolescents (1.0 min) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min., respectively). The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. Comparing within paediatric age groups demonstrated that mean time to reappearance of T3 was prolonged in neonates and infants (56.7 and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 min., respectively).

Mean SD time to onset and clinical duration following 0.6 mg/kg rocuronium initial intubation dose* during sevoflurane/nitrous oxide and isoflurane/nitrous oxide (maintenance) anaesthesia (Paediatric patients) PP group.

	Time to maximum block** (min)	Time to reappearance of T3** (min)
Neonates (0 - 27 days) n = 10	0.98 (0.62)	56.69 (37.04) n=9
Infants (28 days - 2 months) n=11	0.44 (0.19) n=10	60.71 (16.52)
Toddler (3 months–23 months) n=28	0.59 (0.27)	45.46 (12.94) n=27
Children (2-11 years) n = 34	0.84 (0.29)	37.58 (11.82)
Adolescents (12-17 years) n = 31	0.98 (0.38)	42.90 (15.83) n = 30

*Dose of rocuronium administered with 5 seconds

** Calculated from the end of administration of the rocuronium intubating dose

Geriatric patients and patients with hepatic and biliary tract disease and/or renal failure
The duration of action of maintenance doses of 0.15 mg.kg^{-1} rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes) (See also section 4.2). No accumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

Intensive Care Unit
Following continuous infusion in the Intensive Care Unit, the time to recovery of the train of four ratio to 0.7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T_2 to train of four stimulation and recovery of the train of four ratio to 0.7 approximates 1.5 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

Cardiovascular surgery
In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg.kg^{-1} rocuronium bromide are a slight and clinically insignificant increase in heart rate up to 9% and an increase in mean arterial blood pressure up to 16% from the control values.

Reversal of muscle relaxation
The action of rocuronium can be antagonised either by Sugammadex or by acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium). Sugammadex can be given for routine reversal (at 1-2 post-tetanic counts to reappearance of T_2) or immediate reversal (3 minutes after rocuronium bromide administration). Acetylcholinesterase inhibitors can be administered at reappearance of T_2 or at the first signs of clinical recovery.

5.2 Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time course runs in three exponential phases. In normal adults, the mean (95%CI) elimination half-life is 73 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193-214) ml.kg^{-1} and plasma clearance is 3.7 (3.5-3.9) ml.kg^{-1}.min^{-1}.

In controlled studies the plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1ml.kg^{-1}.min^{-1} (see section 4.2).

Paediatric Patients
Pharmacokinetics of rocuronium bromide in paediatric patients (n=146) with ages ranging from 0-17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance (1.hr^{-1}kg^{-1}). The volume of distribution (l.kg^{-1}) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarized below:

Estimated PK parameters [Mean (SD)] of rocuronium bromide in typical paediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/Nitrous oxide (maintenance anaesthesia)

		Patient	Age	Range	
Pk Parameters	Term Newborn infants (0-27 days)	Infants (28 days to 2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (12-17 years)
CL L/kg/hr	0.31 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of distribution (L/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
$T_{½}$ β (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large between patient variability is found in controlled clinical studies, related to nature and extent of (multiple) organ failure and individual patient characteristics.

In patients with multiple organ failure a mean (± SD) elimination half-life of 21.5 (± 3.3) hours, a (apparent) volume of distribution at steady state of 1.5 (± 0.8) $l.kg^{-1}$ and a plasma clearance of 2.1 (± 0.8) $ml.kg^{-1}.min^{-1}$ were found. See also Posology and method of administration.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as the parent compound. No metabolites are detected in plasma.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Acute toxicity:
In acute toxicity studies rocuronium bromide was intravenously administered to cats and dogs up to a dose of 350 x ED90 and 750 x ED90 respectively. This last dose was administered in 4 consecutive doses at intervals of 30 minutes (9, 18, 36 and 72 mg per kg body weight) and resulted in death due to cardiac collapse.

Subacute toxicity:
In subacute toxicity studies rocuronium bromide was intravenously administered to cats and dogs up to a dose of 37 x ED90 and 60 x ED90 respectively two times per week for a period of 4 weeks. Unforeseen mortalities occurred in three out of seven dogs at the dose of 60 x ED90 (10.8 mg per kg body weight). The cause of death could not be established, but was considered to be related to interactions between rocuronium treatment and experimental procedures and/or instrumentation and anaesthesia.

Chronic toxicity:
Chronic toxicity studies have not been performed with rocuronium bromide.

Mutagenicity and carcinogenicity:
One Ames Test showed a dose related increase in the number of his + revertants with S. typhistrain TA98. No mutagenic potential was noted in further in vitro and in vivo testing. Therefore the biological relevance of the weak response in this test is regarded as insignificant.

Carcinogenicity studies have not been performed with rocuronium bromide.

Reproductive toxicity:
Studies in rats with administration of rocuronium bromide during organogenesis using subpharmacological intravenous doses revealed no evidence of embryolethality, teratological changes or suppression of growth of the foetuses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Sodium chloride
Glacial acetic acid (for pH adjustment)
Water for injections.

6.2 Incompatibilities

Physical incompatibility has been documented for Esmeron when added to solutions containing the following drugs: amphotericin B, amoxycillin,azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, frusemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Esmeron must not be mixed with other medicinal products except those mentioned in section 6.6. If Esmeron is administered via the same infusion line that is also used for other drugs, it is important that this infusion is adequately flushed (e.g. with 0.9% NaCl) between administration of Esmeron and drugs for which incompatibility with Esmeron has been demonstrated or for which compatibility with Esmeron has not been established.

6.3 Shelf life

Unopened: 3 years.

After opening the vial: Use immediately and discard any unused contents.

After dilution: diluted product (see section 6.6 for possible infusion fluids) should be used immediately and any unused contents should be discarded.

6.4 Special precautions for storage

Store in the refrigerator (2ºC to 8ºC). The product can be stored outside the refrigerator at a temperature of up to 30ºC for a maximum of 3 months. The product may be placed in and out of the refrigerator at any point(s) during the 36 months shelf life, but the total storage time outside the refrigerator must not exceed 3 months. The storage period may not exceed the labelled shelf life.

6.5 Nature and contents of container

2.5ml, 5ml or 10ml Type 1 Ph.Eur., clear, colourless, glass vial with a rubber closure and flip-off cap.
Pack sizes: 25mg/2.5ml – 10 vials, 50mg/5ml - 10 vials, 100mg/10ml-10 vials.

The rubber stopper of the vial does not contain latex.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Esmeron has been shown to be compatible with the following infusion fluids:

0.9% Sodium Chloride Intravenous Infusion
5% Glucose Intravenous Infusion
5% Glucose and 0.9% Sodium Chloride Intravenous Infusion
Water for injections
Lactated Ringers Solution
Haemaccel 35.

For single use only. Unused solutions should be discarded.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1286/058/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 August 1996

Date of last renewal: 07 August 2006

10 DATE OF REVISION OF THE TEXT

February 2026